12. (Amended) The method according to claim 7, wherein the vasomotor symptom is hot flushes.

69. (Amended) The method according to claim 7, wherein the daily dosage of conjugated equine estrogens, USP is about 0.45 mg.

REMARKS

Claims 1-7, 11, 12, and 15-69 are now pending in the above-referenced application. Applicant acknowledges that claims 1-6 and 15-68 have been withdrawn from consideration pursuant to the election made by Applicant in the Amendment under Rule 111, dated December 13, 2001. Applicant has rewritten claim 10 in independent form (as claim 7) and respectfully requests allowance of this claim and any claim dependent thereon.

In the Office Action mailed March 12, 2002, Claims 7-14 and 69 were rejected under 35 U.S.C. § 103 as allegedly unpatentable over U.S. Patent No. 4,826,831, Re 36,247 (hereinafter, "Plunkett"). In order to expedite prosecution of this application, Applicant has cancelled claims 8-10, 13 and 14, and has rewritten claim 10 (now designated claim 7) in independent form. Applicant does not acquiesce in the rejection of the canceled claims, and reserves the right to pursue such subject matter in other applications. In rejecting claims 7-14 and 69, the Examiner relies on the reference in Plunkett to combining conjugated equine estrogens ("CEE") with medroxyprogesterone acetate ("MPA"), listed among nineteen other possible estrogen/progestin combinations. Plunkett also claims such a combination in the context of a cyclical administration of estrogen, in addition to a continuous uninterrupted combined administration of estrogen and progestin. (See Plunkett, claim 8).

The pending claims of the present application are drawn specifically to continuously and uninterruptedly providing a daily using a dosage of about 1.5 mg MPA in combination with a dosage of between about 0.3 and about 0.45 mg CEE, USP. This specific dosage of MPA in combination with CEE is nowhere specified in Plunkett. In particular, Plunkett does not describe or suggest a daily dosage of about 1.5 mg MPA at all, much less in combination with the claimed dosage of CEE.

Plunkett describes 0.600 mg as the preferred dosage of CEE (Plunkett, Table 1A) and 2.5 mg as the preferred dosage of MPA (Plunkett, Table 1B) - dosages which are far higher than the 1.5 mg of MPA and the about 0.3 to about 0.45 mg of CEE claimed in the present application. Indeed, as described in the application, it was unexpectedly demonstrated by clinical studies that providing a daily dosage of 1.5 mg MPA in combination with CEE in the claimed ranges would effectively inhibit the development of endometrial hyperplasia. It was furthermore unexpected that the claimed dosage combination of CEE and MPA rapidly reduced the number and severity of hot flushes to essentially the same extent as a much higher dose combination containing 0.625 mg CEE and 2.5 mg MPA.

The findings from the clinical studies provide evidence for a therapeutic role for MPA beyond endometrial protection, when lower dosages of CEE are used. (See Utian et al., Fertility & Sterility, 75(6):1065-1079 (2001)). This new evidence suggests that dosages of CEE combined with MPA, along the lines of the invention, may be better than equivalent dosages of unopposed CEE for vasomotor symptom relief. These results are in contrast with prior studies with the most common dosages of CEE, which reported no additional effect of MPA on vasomotor symptom relief. (See Greendale et al., Obstet. Gynecol., 92:982-988 (1998)). While not wishing to be bound by theory, at low CEE dosages, MPA may enhance the efficacy of CEE in relieving vasomotor symptoms. Thus, Applicant's invention may create a significant benefit for a patient while reducing the risks.

In rejecting a claim under 35 U.S.C. § 103(a), the Examiner bears the initial burden of presenting a prima facie case of obviousness. In re Rijckaert, 9 F.3d 1531, 1532, 28 U.S.P.Q.2d 1955, 1956 (Fed. Cir. 1993). To establish prima facie obviousness, the prior art reference(s) must teach or suggest all of the claim limitations. In re Royka, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974). Because Plunkett does not teach, or suggest, using 1.5 mg MPA in combination with about 0.3 to about 0.45 mg CEE for relief of vasomotor symptoms of menopause, it is respectfully submitted that Plunkett does not render claim 7 obvious.

Moreover, it is respectfully submitted that In re Fine, supra, makes plain that the Office Action's generalized assertions that it would have been obvious to modify the reference does not properly support a § 103 rejection. It is respectfully submitted that the

Office Action reflects an inappropriate "obvious to try" standard, and therefore does not reflect the proper evidence to support an obviousness rejection based on the references relied upon. In particular, the Court in the case of In re Fine stated that:

> The PTO has the burden under section 103 to establish a *prima facie* case of obviousness. It can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. This it has not done. . . .
>
> . . . .
>
> Instead, the Examiner relies on hindsight in reaching his obviousness determination. . . . One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.

In re Fine, 5 U.S.P.Q.2d at 1598 to 1600 (citations omitted; italics in original).

That is exactly the case here, since it is believed and respectfully submitted that the Office Action offers no evidence, but only conclusory hindsight, reconstruction and speculation.

There is no evidence that Plunkett provides the features and benefits specified by the invention of claim 7. Specifically, Plunkett does not recognize the importance of balancing the dosages of MPA and CEE at any levels, much less that the selection of 1.5 mg MPA would provide the beneficial results achieved in combination with about 0.3 to about 0.45 mg CEE. It is therefore respectfully submitted that claim 7 is allowable for these reasons.

Claims 11, 12 and 69 depend from claim 7, and it is respectfully submitted that Plunkett does not render obvious these dependent claims for at least the same reasons given above in support of the patentability of claim 7.

Attached hereto is a marked-up version of the changes made to the claims by the current Amendment. The attached page is captioned "**Version with Markings to Show Changes Made**."

Applicant has been contacted by a third party regarding the inventorship of this application. The third party has stated that he believes himself to be an inventor of subject matter disclosed in the application. Applicant has investigated the inventorship of the subject matter disclosed in this application and has undertaken an initial exchange of documents and information with the third party. Pursuant to its investigation on this matter, Applicant has determined that James Pickar and Michael S. Dey, employees of Wyeth, are the joint inventors of this application and that Mr. Dey previously was inadvertently omitted as an inventor. Concurrently with filing the RCE and this Amendment, Applicant is submitting a petition to correct the inventorship of this application under 37 C.F.R. § 1.48(a) by adding Mr. Dey as an inventor. Based on the information gathered to date, Applicant does not believe that the third party is an inventor of the subject matter claimed herein. Applicant has requested a written statement from the third party detailing the reasons why the third party believes he may be an inventor. To date, the third party has not provided such a statement. While Applicant believes that the third party is not an inventor of the subject matter claimed in the application, Applicant plans to make an additional submission to the PTO with further details after undertaking additional investigation, so that the PTO, pursuant to 35 U.S.C. § 116, may provide its determination regarding the inventorship of the application. Applicant will again seek the third party's written submission and will provide such to the PTO when obtained.

It is therefore respectfully submitted that all pending claims are allowable. All issues raised by the Examiner having been addressed, reconsideration and allowance of the claims are respectfully requested. If for any reason the Examiner believes that contact with Applicant's attorney would advance prosecution, he is invited to contact the undersigned at the telephone number given below.

Respectfully Submitted,

Dated: 9/5/02

By: _____

Arnold S. Milowsky
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

7. (Amended) A method of treating or inhibiting vasomotor symptoms in a perimenopausal, menopausal, or postmenopausal women in need thereof, which comprises orally providing to said woman continuously and uninterruptedly over the treatment period, a combination of conjugated equine estrogens, USP and a daily dosage of about 1.5 mg of medroxyprogesterone acetate, wherein the daily dosage of conjugated equine estrogens is between about 0.45 mg and about 0.3 mg.

11. (Amended) The method according to claim [10] 7, wherein the daily dosage of conjugated equine estrogens, USP is about 0.3 mg.

12. (Amended) The method according to claim [8] 7, wherein the vasomotor symptom is hot flushes.

69. (Amended) The method according to claim [10] 7, wherein the daily dosage of conjugated equine estrogens, USP is about 0.45 mg.